

REMARKS

Claims

Claims 10–13 are currently under examination with claims 1–9 and 14–17 withdrawn from consideration due to restriction/election. Claims 18–20 are added by this paper.

Claim amendments

The claims have been amended according to conventional US practice. For example, use claim 13 has been amended to recite US process claim.

New claim 18 is supported by the disclosure contained in, for example, the ABSTRACT and page 1, lines 13–19 of the originally-filed specification. Support for new claim 19 can be found in original claim 9 and page 9, lines 5–7 of the originally-filed specification (i.e., an embodiment of the present invention relating to process for the preparation of such polypeptides by cultivation of a host organism and *isolation* of the corresponding polypeptide from the culture).

Claim 20 is supported by the disclosure contained in, for example, paragraph [0075] of the published application.

Applicants respectfully submit that the amendments presented herein do not raise new matter. Entry thereof is earnestly solicited.

Claim objections

The Examiner is thanked for her careful reading of the claims. The objection of claims 10 and 11 is moot in view of the amendment of the claims.

Rejection under 35 U.S.C. §112, ¶1

The forgoing amendments render the rejection of claims 10–13 under this section moot. Withdrawal of the rejection is respectfully requested.

Priority

A certified copy of the German priority document No. DE 103 59 351.9 (filed: December 16, 2003) was furnished with the original application papers and received by the USPTO on June 15, 2006. A certified English translation of the priority document is enclosed herewith.

Rejections under 35 U.S.C. §112, ¶1

Claims 10–12 are rejected due to allegedly lacking sufficient written description of the

polypeptide species. Additionally, claims 10–12 are rejected under this section as allegedly lacking enablement with respect to the use of the polypeptides of the present invention as pharmaceutical compositions. These rejections are both respectfully traversed.

Written description rejection

Applicant has reviewed the PTO's new Written Description Guidelines and maintains that the present claims are in accordance with Example 10 beginning on Page 33 of the *Training Materials* (Rev. 1, March 25, 2008). See also, Example 6 at page 21 of the Guidelines. While applicants may not agree with the agency's interpretation of the elements necessary to meet the statutory requirements of 35 U.S.C. § 112, ¶1, nonetheless, the pending claims have been amended to substantially conform to these.

The PTO's example provides a claim to a protein isolated from mouse liver that catalyzes the reaction A->B. The isolated protein was sequenced and its sequence was set forth in the specification as SEQ ID NO: 3.

- Claim 1. An isolated protein comprising the amino acid sequence shown in SEQ ID NO: 3.
- Claim 2. An isolated variant of a protein comprising the amino acid sequence shown in SEQ ID NO: 3, wherein the variant comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 3.

The guidelines state that claims 1 and 2 satisfy the requirements set forth under §112, ¶1. The Examiner's statements, for example, in the second paragraph under item 11 at page 9 of the present Office Action further corroborates with the written description guidelines. Thus it is respectfully submitted that the foregoing amendments render moot the written description rejection. The polypeptides are now claimed in terms of specific sequences. This is not to imply that the original claim scope was problematic under US law. Withdrawal of the rejection is respectfully requested.

Enablement

In the paragraphs bridging pages 5 and 8, the Office Action alleges that the pharmaceutical compositions are non-enabled. This contention is respectfully traversed.

At page 5 of the Office Action, the rejection begins with a recitation of the so-called *Wands* factors. The Examiner asserts that these are the factors to consider when determining whether a disclosure satisfies the enablement requirement under 35 U.S.C. §112, ¶1. However, this is not an accurate description of the analysis of the *Wands* factors.

The *Wands* factors are to be used for determining whether undue experimentation is

required for enablement. As expressly stated by the court in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), “Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented,” However, before the issue of undue experimentation arises, the rejection first must present reasons to doubt the veracity of the enablement statements presented in the specification.

Applicants’ specification, coupled with a skilled worker’s knowledge, provides more than adequate guidance on how to make the claimed polypeptide molecules and use pharmaceutical compositions and medicaments comprising such polypeptides for immunotherapy. The specification provides both general and specific guidance regarding the specific epitopes in allergens and how such could be manipulated for reliable hyposensitisation. See, for example, the disclosure contained in the paragraphs bridging pages 6 and 7 of the instant specification and the reference article by Schramm et al., 1999, J. Immunol. 162: 2406-2414. With respect to DNA vaccines, the specification explicitly teaches that “experimental evidence of allergen-specific influencing of the immune response has been furnished in rodents by injection of allergen-encoding DNA (Hsu et al., 1996, Nature Medicine 2 (5): 540-544).” As such, the PTO’s contentions regarding non-enablement of the claimed pharmaceutical compositions are without merit.

Furthermore, the specification of the present application discloses specific immunotherapy or desensitization as therapeutic field for especially recombinant allergen proteins with higher purity and therefore reduced side effects than allergen proteins isolated from natural sources which are always mixtures of compounds. In any event, existence of side effects, if any, is not relevant to the PTO considerations. See, *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969). To this end, the specification discloses strategies to minimize the risks of side effects with the development of T-cell reactive fragments with reduced or no IgE-reactivity leading to hypoallergenic peptides (see, see, the paragraph bridging pages 7 and 8 of the originally-filed specification). The screening for T-cell and IgE epitopes were common knowledge at the priority date of the present application. Thus, a person skilled in the art would have been able to identify T-cell and IgE epitopes and produce hypoallergenic peptides. Nevertheless, also the classic approaches of specific immunotherapy and desensitization were applicable as a skilled person would have known the pharmaceutical effects and also the side effects and risks of an allergen protein administered to a patient and would have followed clinical recommendation protocols for specific immunotherapy and desensitization.

In relation to an enabling disclosure on the utilization of grass pollen allergen polypeptides in treatment of subjects, the specification provides a detailed disclosure for the design, synthesis and use of recombinant allergen extracts with reduced IgE reactivity. See, for example, the first

paragraph on page 6 of the originally-filed specification. To this end, the Examiner is also courteously invited to review the disclosure contained in the enclosed Focke et al. (*FASEB Journal*, vol. 15, 2042-44, 2001). As evidenced by the disclosure in the “Immunization” section of Focke et al. and the immunoglobulin reactivity data provided in Figs. 5 and 6 and Tables 3–5 of the article, it is respectfully submitted that as of the filing date of the present application, the instantly claimed grass pollen allergens could be routinely manipulated and utilized as pharmaceutical preparations in a manner recited in the claims.

Thus, it is respectfully submitted that the specification provides an enabling disclosure on the claimed allergenic properties of the recombinant, grass pollen allergen polypeptides of the instant invention. Therefore, the specification’s express teaching that the claimed compounds are pharmaceutically useful is clearly credible as required. The PTO’s contentions regarding non-enablement are especially weak in view of the detailed disclosure contained in Applicants’ own specification and the state of the art before the earliest filing date of the instant application. Withdrawal of the rejection is respectfully requested.

To support the contention of non-enablement, the Office Action cites Tarzi (*Expert Opinion in Biol. Ther.*, 2003) to allege that “whole allergen immunotherapy is unpredictable.” See the paragraph bridging pages 7 and 8 of the present Office Action. However, even Tarzi discloses the therapy of allergic diseases with specific immunotherapy or desensitization in general being effective and successfully applied for many years. See, the last paragraph at page 617 of the cited reference. As such, the PTO’s contentions of non-enablement, based on the disclosure contained in Tarzi et al., are without merit.

The Office Action at page 9 alleges that it would “take undue trials and errors to practice the claimed invention.” These allegations, however, do not present any evidence to doubt the objective enablement of Appellants’ disclosure. As clearly and succinctly stated by the court in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

As a matter of Patent Office practice, then a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken in compliance with the enabling requirement of the first paragraph of §112, **unless** there is reason to doubt the objective truth of statements contained therein relied on for enabling support. (emphasis in original)

Furthermore, as stated in *Marzocchi*, at 370, the PTO must have adequate support (evidence or reasoning) for its challenge to the credibility of Appellants’ statements of enablement. Thus, in the absence of evidence which demonstrates otherwise, the claims must be taken to satisfy the

requirements of 35 U.S.C. § 112, ¶1.

Working examples are not required to establish enablement. As stated by the court *Marzocchi*, at page 369:

The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The assertion of undue experimentation in the rejection is merely conclusory. Further, as discussed above, the specification provides more than sufficient guidance to make and use the claimed medicaments and/or pharmaceutical compositions using no more than routine experimentation. Finally, a high level of skill does not establish that one skilled in the art would have reasons to doubt the veracity of the statements in Appellants' specification with respect to the use of the claimed composition in the diagnosis, treatment, and/or prevention of the claimed conditions.

Alleged lack of *in vivo* data and other clinical data

The Office Action at page 4 alleges that "there is no evidence provided by the instant specification that the instant compounds have been used to treat [indications] *in vivo*." It is further alleged that "there is no data within the instant specification to show that these compounds have been successfully used to treat any of these conditions or that the compounds are well-tolerated." These contentions are without legal basis.

At the outset, Applicants courteously submit that the Office Action fails to present any evidence which suggests the methods claimed herein are not enabled. In the absence of such evidence, the rejection is deficient under controlling case law.

The burden is upon the Patent and Trademark Office to provide evidence shedding doubt that the invention can not be made and used as stated; see for example, *In re Marzocchi*, 439, F. 2d 220, 169 USPQ 367 (CCPA 1971). Moreover, decades of scientific studies, both at the basic and clinical levels, have established that *in vitro* studies "reasonably correlate" with their *in vivo* counterparts. There is no basis for the general allegation that "clinical correlations are generally lacking" for *in vitro* assays and/or cell-culture based assays.

Furthermore, the patent law is in accord with the realities of pharmaceutical arts.

In *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985), discussed *supra* the court affirming the decision on reliance on *in vitro* data, and the decision stated that

in vitro results with respect to the particular pharmacological activity are generally predictive of *in vivo* test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. (Emphasis added)

The court in *Cross* decision also noted the following

Knowledge of the pharmacological activities of compounds is beneficial to the medical profession, and requiring Iizuka to have disclosed in vivo dosages in the Japanese priority application would delay and frustrate researchers by failing to provide an incentive for early public disclosure of such compounds, thereby failing to further the public interest.

...
Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. (Emphasis added)

The Federal Circuit in *Fujikawa v. Watanasin*, 39 USPQ.2d 1895 (1996), stated that

all that is required is the test to be reasonably indicative of the desired pharmacological response. ... There must be a sufficient correlation between the tests and the asserted pharmacological activity so as to convince those skilled in the art, to a reasonable probability, that the novel compound will exhibit the asserted pharmacological behavior.

Also, the court in *Brana* 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) stated that

it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Applicants also point to *In re Bundy*, 642 F.2d 430, 209 USPQ 48, (CCPA 1981), where the disclosure established the basic pharmacology for the compounds, but where no examples were provided. The *Bundy* specification stated that the compounds of the invention possessed activity similar to E-type prostaglandins. Nevertheless it was found that sufficient guidance as to use were given in the disclosure. The court held that “what is necessary to satisfy the how-to-use requirement of §112 is the disclosure of some activity coupled with knowledge as to the use of this activity.”

Thus, neither the reality of the pharmaceutical arts or industry or the state of the law in this area provide basis for the broad allegations on pages 6 and 7 of the Office Action. Thus, the rejection is without merit and should be withdrawn.

Based on the aforementioned remarks and arguments, further in view of the amendments presented herein, it is respectfully submitted that Applicants' specification provides an enabling disclosure of what is claimed by the present invention. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

Rejections under §102 (a)/§103(a)

Claims 10-12 are rejected under §102(a) as allegedly anticipated by EMBL Accession Nos. AJ862830 (accessioned: November 19, 2004); AJ862831 (accessioned: November 19, 2004); AJ862832 (accessioned: November 19, 2004); AJ862833 (accessioned: November 19, 2004) or AJ862834 (accessioned: November 19, 2004). The instant application claims priority to DE 103 59 351.9 (filed: December 16, 2003). The disclosure in the priority application supports the instant claims. See, the disclosure in page 4 and the Examples section of the enclosed translation of the priority document, along with the sequence listing appended thereto. As such, the rejections should be withdrawn.

In view of the foregoing arguments, it is submitted that the obviousness rejection of claims 10 and 12–13 over one or more of the aforementioned EMBL accession Nos. in view of the disclosure in US patent application publication 2006/0177470 cannot stand. Withdrawal of the rejection is respectfully requested.

Rejection under §102(e)

Claims 10–13 are rejected under 102(e) as allegedly anticipated by WO 04/000881 (published in German; published: December 31, 2003), as evidenced by the disclosure in the present specification at page 3, lines 35–36. The earliest effect date of this reference is the §102(a) date, which is the publication date of the WO 04/000881 (i.e., December 31, 2003). It is submitted that this date is after the priority date of the instant application, and as such, the rejection cannot stand. See, *supra* regarding the disclosure in the priority document.

Rejection under §102(b)

Claims 10–12 are rejected under 102(b) as allegedly anticipated by Gavrovic (*Allergy*, 1998), as evidenced by the disclosure in the present specification at page 4, lines 1–22. The Office Action alleges that the specification at page 4 teaches that Sec c4 is the allergen isolated from *Secale cereale* having the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The Office Action further reasons that the reference teaches the same isolated allergen from the same source, so the resulting allergen must necessarily have the sequence of SEQ ID NO: 2 or SEQ ID NO: 4. This line of nebulous reasoning is respectfully traversed.

The rejection is based on the references' disclosure of allergens from *Secale cereale*. The Office Action has not established that such polypeptides are structurally and/or functionally identical to the polypeptide(s) comprising the sequences set forth in SEQ ID NOS. 2, 4, 6, 8, or 10, as claimed

herein. More specifically, the totality of the disclosure in Gavrovic says nothing about the identity of the polypeptides of the present invention which are currently claimed. Absent such, the reference cannot anticipate what is claimed herein.

Moreover, allergen proteins obtained from natural sources are always mixtures of several compounds and allergens isolated therefrom do not normally contain pure protein. This is the advantage of recombinantly prepared proteins and the subject matter of the present invention. Thus, the polypeptides claimed herein are not inherent in the reference, as the references do not disclose the recited sequences. See, the subject matter of the new claims. As such, the PTO's contentions are without merit.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to
Deposit Account No. 13-3402.

Respectfully submitted,

/Anthony J. Zelano/

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicant(s)

/Sagun KC/

Reg. No. L0510

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-3178

Date: March 25, 2009